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Longitudinal association between markers of liver injury and mortality in COVID-19 in China

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Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; CoV-2, coronavirus 2; COVID-19, coronavirus disease 2019; CT, computed tomography; IQR, interquartile range; SARS, severe acute respiratory syndrome; TBIL, total bilirubin; ULN, upper limit of normal.

Abstract

Coronavirus disease 2019 (COVID-19) is a new infectious disease. To reveal the hepatic injury related to this disease and its clinical significance, we conducted a multicenter retrospective cohort study that included 5,771 adult patients with COVID-19 pneumonia in Hubei Province. We reported the distributional and temporal patterns of liver injury indicators in these patients and determined their associated factors and death risk. Longitudinal liver function tests were retrospectively analyzed and correlated with the risk factors and death. Liver injury dynamic patterns differed in alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin (TBIL). AST elevated first, followed by ALT, in severe patients. ALP modestly increased during hospitalization and largely remained in the normal range. The fluctuation in TBIL levels was mild in the non-severe and the severe group. AST abnormality was associated with the highest mortality risk compared to other indicators of liver injury during hospitalization. Common factors associated with elevated liver injury indicators were lymphocyte count decrease, neutrophil count increase, and male gender. *Conclusion:* The dynamic patterns of liver injury indicators and their potential risk factors may provide an important explanation for the COVID-19-associated liver injury. Because elevated liver injury indicators, particularly AST, are strongly associated with the mortality risk, our study indicates that these parameters should be monitored during hospitalization.

Coronavirus disease 2019 (COVID-19) is a viral respiratory illness caused by a novel coronavirus (nCoV). COVID-19 is highly contagious, with more than 2.3 million cases and nearly 163 thousand deaths worldwide on April 21, 2020.[1, 2] The targeting organs of this coronavirus are believed to be the lungs and airways. However, patients often have evidence of damage to other organs, which significantly increases their mortality.[3, 4] The pathophysiological foundation of multiorgan damage may be associated with organ-specific immune response to disseminated coronavirus or secondary to hypoxemia, systemic cytokine storm, and medication.[5] In an attempt to determine the distributional and temporal patterns of liver injury in patients with COVID-19 with a focus on clinical significance and determinants of this change, we conducted a multicenter retrospective cohort study that included 5,771 patients in Hubei Province.

Methods

Study design and participants

In this multicenter retrospective cohort study, patients with COVID-19 were admitted to the following 10 hospitals that were designated to treat COVID-19 patients: Renmin Hospital of Wuhan University, Thunder Mountain Hospital, Wuhan Ninth Hospital, Huanggang Central Hospital, Zhongnan Hospital of Wuhan University, Wuhan Central Hospital, Wuhan Third Hospital, Wuhan Seventh Hospital, Wuhan First Hospital, Central Hospital of Enshi Tujia and Miao Autonomous Prefecture. A total of 7,029 adult patients admitted to hospitals from December 20, 2019, to March 8, 2020, were enrolled in the study. Exclusion criteria, which applied to 1,258 patients, were as follows: age younger than 18 or older than 75 years; pregnancy; severe medical conditions, including liver cirrhosis (10 cases), chronic renal dysfunction (above chronic kidney disease stage 3 [CKD 3]), leukemia, cancer, acquired immune deficiency syndrome, acute myocardial infarction during hospitalization, acute pulmonary embolism (due to a long-term pulmonary embolism disease history, long-term bed rest, and coagulopathy) stoke, and acute pancreatitis; or transfer to other hospitals (Fig. 1).

Chest computed tomography (CT) or throat-swab specimens were obtained from all patients upon admission. COVID-19 was diagnosed by clinical manifestations, chest CT, or real-time polymerase chain reaction (RT-PCR) according to World Health Organization (WHO) interim guidance and the New Coronavirus Pneumonia Prevention and Control Program (5th edition) published by the National

Health Commission of China. At the time of admission, patients with fever or suspected respiratory infection, plus one of the following clinical manifestations including respiratory rate greater than 30 breaths/minute, severe respiratory distress, or oxygen saturation (SpO_2) less than 90% on room air, were classified as severe cases.[6] Staging of COVID-19 and evaluation of organ damages were conducted by a team of physicians. This study was approved by the central institutional ethics committee and ratified by each hospital. A waiver of the requirement for documentation of informed consent was granted for analyzing existing data without interfering with patient treatment.

Procedures and complication evaluation

The demographic, clinical characteristics, medical history, laboratory tests, radiological reports, therapeutic intervention, and outcome data were obtained from patients' electronic medical records. Clinical symptoms, including fever, cough, fatigue, dyspnea, and comorbidities, were extracted. The laboratory examination included a complete blood count, C-reactive protein (CRP), procalcitonin, D-dimer, and serum biochemical tests for liver, kidney, heart, and coagulation dysfunction. Medical history comprised coexistence of chronic obstructive pulmonary disease (COPD), type 2 diabetes mellitus (T2DM), hypertension, coronary heart disease, cerebrovascular disease, chronic liver disease, CKD, cancer, and autoimmune diseases. The unilateral and bilateral lesions in chest CT scan images were recorded and analyzed. Personal identification information (e.g., name and ID) of the study subjects was anonymized and replaced with a coding system before data extraction. Data were reviewed and confirmed by experienced physicians and double-checked to ensure accuracy.

Acute lung injury (ALI), acute respiratory distress syndrome (ARDS), and septic shock were defined according to the WHO interim guideline for "clinical management of severe acute respiratory infection when novel coronavirus (2019-nCoV) infection is suspected."[4] Acute kidney injury was defined as an elevation in serum creatinine level ≥26.5 μmol/L within 48 hours.[7] Acute liver injury was defined as the levels of serum alanine aminotransferase (ALT) above 3-fold of the upper limit of normal (ULN). Increase in liver enzyme levels was defined as the levels of serum liver enzyme above the ULN. Cardiac injury was defined as the serum level of cardiac troponin I/T or hypersensitive troponin I/T above the ULN.[8] Clinical Disseminated Intravascular Coagulation (DIC) was defined according to the International Society on Thrombosis and Haemostasis (ISTH) criteria for diagnosing

DIC.[9] The primary endpoint was recorded and evaluated in this longitudinal cohort, which was 28-day all-cause death. Data were reviewed and confirmed by two certified physicians to ensure accuracy.

Statistical analysis

Categorical variables were presented as frequency. Continuous variables were described as median (interquartile range [IQR]). Means for continuous variables were compared using independent group *t* tests when the data were normally distributed; otherwise, the Mann-Whitney test was used. Proportions for categorical variables were compared using the Chi-square test. Proportions for categorical variables were compared using the Chi-square test or Fisher exact test. Distribution of highest liver enzyme levels (e.g., ALT, AST, ALP, and TBIL) by the severity of COVID-19 was presented using kernel density estimation. Dynamic changes of liver enzyme levels by the severity of COVID-19 were presented using locally weighted scatterplot smoothing (LOESS). Site was modeled as a random effect in the mixed-effect Cox model. The mixed-effect Cox proportional hazards regression models were used to investigate the relationship of liver enzyme levels with all-cause mortality among patients. The mixed-effect Cox models were adjusted for age, gender, and coexisting chronic diseases, including hypertension, coronary artery disease, cerebrovascular disease, T2DM, and CKD. Ordinal logistic regression analysis was applied to evaluate the association of baseline characteristics and medications happened before peaking of liver enzymes with the peak levels of in-hospital liver enzymes in the longitudinal cohort, where the liver function markers were trichotomized. The parallel lines assumption of the model was also tested and met. The *P* values were 2-sided, and an alpha level of 0.05 was used to define statistical significance. All analyses were conducted using R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria) or SPSS version 23.0 (IBM, Armonk, NY, USA).

Results

Patient Population

The selected baseline liver characteristics of the enrolled patients are shown in Table 1. A total of 5,771 adult patients with COVID-19 were included in the analysis. The median age was 56 (IQR, 43-

65 years), and 2,724 (47.2%) were male (Supporting Table S1-S2). Among these patients, 4,585 (79.4%) were non-severe cases and 1,186 (20.6%) were classified as severe cases. A total of 81 (1.4%) patients reported chronic liver disease. Among these patients, 4 recorded fatty liver diseases and 77 viral hepatitis (Supporting Table S3). The median day for acute liver injury (ALT >3 ULN) occurs at day 17 (IQR, 13-23) after symptom onset (Fig. 1).

Dynamic Profile of Liver Function Indicators in Patients With COVID-19

To determine the distribution and trajectory of parameters indicating liver functions in patients enrolled in the study, multiple results from liver function tests were recorded during hospitalization. Fig. 2A displays peak values of ALT, AST, ALP, and TBIL. Fig. 2B depicts their distributions in patients with non-severe and severe COVID-19. ALT, AST, ALP, and TBIL levels were lower and less disperse in non-severe cases. These levels increased and grew more disperse as the disease became more severe. Non-severe and severe case distribution had widest separation by AST level (Fig. 2B). LOESS models illustrated trajectory of ALT, AST, ALP, and TBIL in non-severe and severe patients during hospitalization (Fig. 2C). The models suggested a significant elevation of AST level upon admission and was maintained at higher levels in the severe group than the non-severe group. Although there was a significant difference in ALT between the non-severe group and the severe group, the magnitude of increase in ALT was not as dramatic as AST upon admission. However, it rapidly increased, surpassed the ULN value, and reached its peak within 10 to 15 days after admission in the severe group. ALP level was higher in the severe group than the non-severe group. Both groups rose gradually during hospitalization but largely stayed in the normal range. The fluctuation in TBIL levels was mild in the non-severe and the severe group. The dynamic changes in indicators suggested potential mechanisms of COVID-19-associated liver injury.

Determining associations between liver function and mortality

Impaired liver function is closely related to mortality in COVID-19 patients. The associations of increased ALT, AST, ALP, and TBIL levels with all-cause mortality were assessed using mixed-effect Cox model. Hospital sites were treated as a random effect. Age, gender, and comorbidities were adjusted as confounders. Hazard ratios for the associations between ALT, AST, ALP, and TBIL and

all-cause mortality are depicted in Table 2. The Kaplan-Meier survival curves with elevation in ALT, AST, ALP, and TBIL levels for all-cause mortality are illustrated in Fig. 3. Among these liver enzymes, elevated AST was associated with the highest mortality risk. Compared to the patients with AST in the normal range, all-cause mortality risk significantly increased 4.81-fold (95% confidence interval [CI], 3.38-6.86; $P < 0.001$) in patients with AST between 40 and 120 U/L and increased 14.87-fold (95% CI, 9.64-22.93; $P < 0.001$) in patients with AST above 120 U/L after adjusting for age, gender, and comorbidities. Moreover, elevation of other enzymes and TBIL were also significantly associated with adverse outcomes of COVID-19 (Table 2 and Supporting Table S4-S5).

Given discharge might be a competing risk for death, we further analyzed the association of liver function with 28-day mortality of COVID-19 using cumulative risk analysis, to further avoid the potential over-estimation of risk in the Hazard estimates. In this model, AST ranging from 40 to 120 U/L and above 120 U/L were associated with significantly increased the risk of all-cause mortality (adjusted HR, 6.00; 95%CI, 4.29-8.39; $P < 0.001$ for 40-120 U/L; adjusted HR, 17.05; 95%CI, 11.21-25.93; $P < 0.001$ for AST >120 U/L) (Supporting TABLE S6)

Associations between clinical characteristics and hospital medication with liver functions

The ordinal regression analysis revealed the effects of age, sex, and coexisting disease–adjusted baseline characteristics and hospital medication on peak ALT, AST, ALP, and TBIL levels in COVID-19 patients from the longitudinal cohort (Tables 3). Male gender, systemic corticosteroids application, lymphocyte count decrease, neutrophil count increase, and fever were factors positively associated with elevated ALT levels (Table 3). Use of antifungal drugs, lymphocyte count decrease, chronic liver disease, systemic corticosteroids use, and male gender were the leading factors positively associated with elevated AST levels. ALP levels were tightly associated with antifungal drug use, neutrophil counts increase, chronic liver disease, and male gender. Antifungal, antiviral, systemic corticosteroids use, and platelet count reduction were main factors positively correlated with increased TBIL levels. Neutrophil count increase, lymphocyte count decrease, and male gender were common factors positively associated with elevated ALT, AST, ALP, and TBIL levels during hospitalization (Table 3).

Discussion

Multiorgan injury, which significantly increases mortality, is often evident in patients with COVID-19.[10] This study presents trajectories of liver enzyme levels during hospitalization and depicts their clinical significance in a multicenter retrospective cohort-derived data set of 5,771 individuals. Liver injury was mild and transient in non-severe patients. The major finding is that elevation of AST level was more frequent and significant than the increase of ALT in severe patients on hospital admission, and AST levels had the highest correlation with mortality compared to other indicators reflecting liver injury. This is contradictory to other hepatitis-induced liver injury. Increase of ALP was more significant toward the latter phase of the disease but mainly stayed within the normal range. Elevated ALT, AST, ALP, and TBIL levels were associated with increased risks of mortality and, among these liver enzymes, elevated AST was associated with the highest mortality risk. Common factors associated with elevated liver injury indicators were lymphocyte count decrease, neutrophil count increase, dyspnea, and male gender.

The liver biopsy specimens of patients with COVID-19 showed moderate microvascular steatosis and mild lobular and portal lesion.[5, 11] Liver damage may be associated with organ-specific immune response to coronavirus or secondary to hypoxemia, systemic inflammation response, and medication. A previous study showed the angiotensin-converting enzyme 2 (ACE2) receptor expression is very low in hepatocytes and only expressed in cholangiocytes in the liver,[12] suggesting that cholangiocytes might be a direct target for severe acute respiratory syndrome (SARS)-coronavirus 2 (CoV-2) invading the liver. However, in our study, ALP, an index of cholangiocytes injury, mainly stayed within the normal range during hospitalization. Elevation in ALT and AST, the indicators of hepatocyte injury, was more common and severe in patients with COVID-19. Pathological analysis of liver tissue from a patient who died from COVID-19 failed to demonstrate cholangiocyte damage and viral infiltration in the liver. The elevations of lactate dehydrogenase (LDH) and gamma-glutamyl transpeptidase (GGT), which also reflect bile duct injury, were not significant.[5] Thus, the hypothesis of cholangiocytes mediating viral-associated injury needs further investigation.

In this study, we observed AST elevation upon admissions, followed by an increase in ALT. Previous studies also reported that AST increase is more frequent than ALT in severe patients upon admission.[3, 13] SARS-CoV-2 differs from other viruses, such as hepatitis B virus (HBV) and SARS,

in which ALT elevation is the primary manifestation of liver injury.[14-16] Ordinal regression analysis also showed that AST elevation is positively correlated with the increase of neutrophil counts and the decrease of lymphocyte counts at baseline—pathological alterations that are proven indicators of disease severity.[17, 18] Early elevation in AST and its association with indicators for disease severity suggest immune-mediated inflammation may play a critical role in liver impairment in severe patients with COVID-19. Mechanisms that mediate the early AST elevation in severe patients warrant further study.

The combination of antibiotics, antivirals, and systemic corticosteroids is widely utilized in COVID-19 treatment.[13, 19] Antifungal medication is more likely to be applied in weaker patients. In this study, use of antifungal drugs, antibiotics, antivirals, and systemic corticosteroids exhibited a positive correlation with elevated liver enzymes. Although these data could not prove the causal effect of drugs on liver damage, drug hepatotoxicity during the treatment of coronavirus infection needs to be considered.

Due to this emergent situation, there is an insufficient report and diagnosis on chronic liver disease. Only 81 patients recorded history of chronic liver disease (4 with nonalcoholic fatty liver disease [NAFLD] and 77 with viral hepatitis), which are much lower than the prevalence in China.[20, 21] We are unable to assess whether coexistence of chronic liver comorbidities increases susceptibility to liver injury in SARS-CoV-2 infection. Previous studies have shown that SARS-CoV-2 may aggravate liver injury in patients with viral hepatitis.[22, 23] Therefore, liver injury in patients with chronic liver disease needs to be investigated and monitored.

Limitations exist in our research. This study was retrospective, and some cases did not have sufficient history of illness. The multiple tests for liver function were carried out at different time intervals for each patient. Bias may occur due to the increased number of tests in patients with liver dysfunction. Observational studies demonstrate association, not causation. Whether abnormal liver function is caused by SARS-CoV-2 or inflammation needs to be further investigated by direct clinical evidence. In conclusion, the dynamic patterns of liver injury indicators and their potential risk factors may provide an important explanation for the COVID-19-associated liver injury. Because the increase of liver injury indicators is strongly associated with the risk of mortality, these parameters, especially AST, may need to be monitored during hospitalization.

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Figure Legends

FIG. 1. Timeline of organ injuries. Bar chart showing median days with interquartile range (IQR) from symptom to acute organ damage. White dots indicate median days; gray/red bars indicate IQR. Abbreviations: ACI, acute cardiac injury; AKI, acute kidney injury; ALI, acute liver injury; ARDS, acute respiratory distress syndrome; DIC, disseminated intravascular coagulation.

FIG. 2. Dynamic profile of liver function in patients with COVID-19 pneumonia. (A) Box plots showing ALT, AST, ALP, and TBIL by severity of the disease. (B) Kernel density estimates using Gaussian kernels to display an overlay of ALT, AST, ALP, and TBIL distributions by disease severity. (C) Smooth trajectories of mean ALT, AST, ALP, and TBIL by disease severity with 95% confidence band based on locally weighted scatterplot smoothing. Patients with fever or suspected respiratory infection, plus one of the following clinical manifestations including respiratory rate greater than 30 breaths/minute, severe respiratory distress, or oxygen saturation (SpO2) less than 90% on room air, were classified as severe cases.

FIG. 3. Kaplan-Meier curves for cumulative probability of COVID-19 mortality during hospitalization in patients with different level of (A) ALT, (B) AST, (C) ALP, and (D) TBIL. ALT1: ALT < 40 U/L; ALT2: ALT = 40-120 U/L; ALT3: ALT > 120 U/L. AST1: AST <40 U/L; AST2: AST = 4-120 U/L; AST3: AST > 120 U/L. ALP1: ALP < 125 U/L (males) and ALP < 135 (females); ALP2: ALP = 125-375 U/L (males) and ALP = 135-405 U/L (females); ALP3: ALP > 375 U/L (males) and ALP > 405 U/L (females). TBIL1: TBIL < 21 μmol/L; TBIL2: TBIL = 21-63 μmol/L; TBIL3: TBIL > 63 μmol/L.

Tables

TABLE 1. Baseline Liver Function of Study Patients

Parameters	Total (n=5771)	Non-severe Patients (n=4585)	Severe Patients (n=1186)	*P* Value
Clinical characteristics				
Age, median (IQR), years	56 (43-65)	55 (42-64)	59 (48-66)	<0.001
Male gender, n (%)	2,724 (47.2%)	2,068 (45.1%)	656 (55.3%)	<0.001
Chronic liver disease, n (%)	81 (1.4%)	56 (1.2%)	25 (2.1%)	0.030
Laboratory examination				
ALT, median (IQR), U/L	24.0(15.1-39.0)	23.0(15.0-38.0)	26.0(17.0-45.0)	<0.001
AST, median (IQR), U/L	24.0(17.0-35.0)	22.0(17.0-31.0)	31.0(21.0-46.0)	<0.001
ALP, median (IQR), U/L	64.0(51.0-83.0)	65.0(51.0-83.0)	63.0(50.0-84.0)	0.630
ALB, median (IQR), g/L	37.5(34.2-40.7)	38.0(34.9-41.1)	35.7(32.2-38.9)	<0.001
GLB, median (IQR), g/L	27.2(24.2-30.4)	27.0(24.0-30.0)	27.8(24.9-31.5)	<0.001
A/G ratio, median (IQR)	1.4(1.2-1.6)	1.4(1.2-1.6)	1.3(1.1-1.5)	<0.001
Total bilirubin, median (IQR), μmol/L	10.4(7.9-14.1)	10.3(7.9-14.0)	10.6(7.9-15.0)	0.053
Direct bilirubin, median (IQR), μmol/L	3.0(2.1-4.4)	2.9(2.0-4.2)	3.3(2.2-5.2)	<0.001
Indirect bilirubin, median (IQR), μmol/L	7.4(5.2-10.3)	7.4(5.3-10.3)	7.1(4.9-10.2)	0.049

Abbreviations: A/G, albumin to globulin; ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GLB, globulin; IQR, interquartile range.

TABLE 2. Associations Between Peak Values of Liver Enzymes and Mortality

	Mixed Cox Crude			Mixed Cox Age, Gender, Comorbidities (Adjusted)		
ALT	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
0-40 U/L	Ref			Ref		
40-120 U/L	2.08	(1.54, 2.81)	<0.001	1.43	(1.04, 1.96)	0.03
>120 U/L	4.70	(3.24, 6.81)	<0.001	3.56	(2.37, 5.37)	<0.001
AST						
0-40 U/L	Ref			Ref		
40-120 U/L	7.44	(5.32, 10.41)	<0.001	4.81	(3.38, 6.86)	<0.001
>120 U/L	21.89	(14.7, 32.59)	<0.001	14.87	(9.64, 22.93)	<0.001
ALP						
M: 0-125 U/L; F: 0-135 U/L	Ref			Ref		
M: 125-375 U/L; F: 135-405 U/L	6.76	(5.05, 9.06)	<0.001	4.24	(3.12, 5.76)	<0.001
M: >375 U/L; F: >405 U/L	8.05	(2.98, 21.77)	<0.001	5.86	(2.03, 16.91)	0.001
TBIL						
0-21 μmol/L	Ref			Ref		
21-63 μmol/L	4.35	(3.32, 5.68)	<0.001	3.28	(2.47, 4.35)	<0.001
>63 μmol/L	9.68	(4.91, 19.07)	<0.001	7.98	(3.88, 16.41)	<0.001

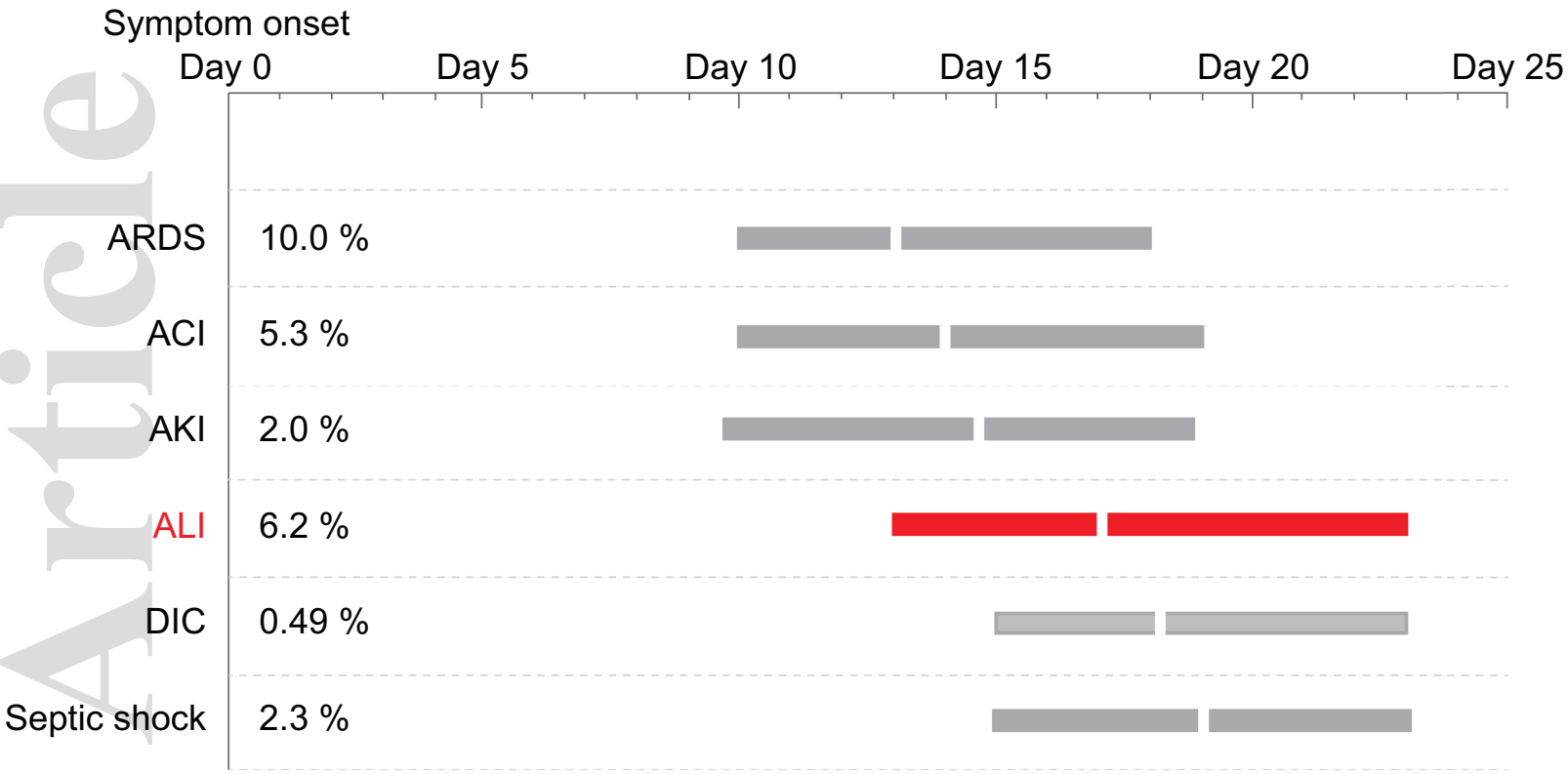
Abbreviations: ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; F, female; GLB, globulin; HR, hazard ratio; IQR, interquartile range; M, male; ref, reference; TBIL, total bilirubin.

TABLE 3. Associations of Patients' Clinical Characteristics at Admission and Hospital Medication with Peak Levels of Liver Function Enzymes

	ALT		AST		ALP		TBIL	
Parameters	**OR (95%CI)**	***P* value**	**OR (95%CI)**	***P* value**	**OR (95%CI)**	***P* value**	**OR (95%CI)**	***P* value**
Age	1.00(0.99,1.00)	0.627	1.02(1.01,1.02)	<0.001	1.02(1.00,1.03)	0.006	1.01(1.00,1.02)	0.011
Male gender	2.36(2.06,2.69)	<0.001	1.60(1.37,1.86)	<0.001	2.00(1.55,2.58)	<0.001	1.52(1.28,1.81)	<0.001
Heart rate	1.00(1.00,1.01)	0.911	1.00(1.00,1.01)	0.46	1.01(1.00,1.02)	0.14	0.99(0.99,1.00)	0.025
Respiratory rate	1.01(0.99,1.03)	0.261	1.02(1.00,1.04)	0.093	1.03(1.00,1.06)	0.08	1.04(1.01,1.06)	0.002
Fever	1.47(1.25,1.72)	<0.001	1.51(1.26,1.81)	<0.001	1.01(0.75,1.36)	0.958	1.11(0.9,1.35)	0.331
Cough	1.02(0.90,1.16)	0.755	0.98(0.85,1.14)	0.804	0.90(0.71,1.15)	0.392	0.99(0.84,1.18)	0.939
Dyspnea	1.37(1.18,1.60)	<0.001	1.41(1.19,1.67)	<0.001	1.28(0.98,1.68)	0.071	1.31(1.08,1.59)	0.007
Gastrointestinal symptoms	1.31(1.10,1.56)	0.002	1.46(1.20,1.77)	<0.001	1.03(0.73,1.45)	0.869	0.92(0.72,1.17)	0.484
Myalgia	1.00(0.83,1.21)	0.996	0.91(0.73,1.13)	0.399	0.90(0.61,1.32)	0.584	0.92(0.72,1.18)	0.526
COPD	0.85(0.40,1.83)	0.683	0.50(0.20,1.26)	0.142	0.17(0.02,1.44)	0.104	0.86(0.34,2.18)	0.748
Cardiovascular metabolic diseases	0.96(0.84,1.11)	0.594	0.98(0.84,1.15)	0.832	1.07(0.83,1.39)	0.581	1.21(1.01,1.45)	0.037
Chronic liver disease	1.61(1.01,2.56)	0.045	1.97(1.20,3.23)	0.007	2.21(1.09,4.50)	0.029	0.95(0.50,1.80)	0.87
Maligancy	1.99(0.48,8.20)	0.339	0.94(0.17,5.26)	0.947	2.31(0.26,20.53)	0.453	0.89(0.10,7.64)	0.915
Chronic kidney disease	0.88(0.53,1.46)	0.625	0.92(0.54,1.58)	0.761	1.82(0.96,3.47)	0.068	0.58(0.29,1.15)	0.117
Lung lesion	1.31(1.15,1.49)	<0.001	1.11(0.97,1.27)	0.142	1.02(0.80,1.29)	0.901	1.10(0.94,1.29)	0.218
Antiviral drug	1.15(0.99,1.33)	0.067	1.00(0.85,1.19)	0.967	1.09(0.81,1.46)	0.565	1.57(1.29,1.92)	<0.001
Antibiotics drug	1.39(1.19,1.63)	<0.001	1.76(1.48,2.11)	<0.001	1.37(1.00,1.87)	0.052	1.17(0.95,1.44)	0.136
Systemic corticosteroids	2.49(2.1,2.94)	<0.001	1.94(1.6,2.35)	<0.001	1.3(0.96,1.76)	0.096	1.60(1.29,1.98)	<0.001
Antifungal drugs	1.59(0.79,3.21)	0.196	2.56(1.23,5.35)	0.012	4.88(2.45,9.73)	<0.001	5.22(2.48,10.99)	<0.001

Neutrophil count > 6.3, 10^9/L	1.42(1.18,1.73)	<0.001	1.60(1.31,1.95)	<0.001	2.43(1.84,3.22)	<0.001	1.58(1.26,1.97)	<0.001
Lymphocyte count < 1.1, 10^9/L	1.56(1.36,1.79)	<0.001	2.21(1.89,2.58)	<0.001	1.71(1.32,2.22)	<0.001	1.28(1.07,1.54)	0.007
Red blood cell	1.23(1.10,1.39)	<0.001	1.30(1.14,1.47)	<0.001	0.90(0.74,1.09)	0.286	1.43(1.24,1.67)	<0.001
Platelet count <100, 10^9/L	1.01(0.80,1.26)	0.964	1.63(1.29,2.06)	<0.001	0.95(0.66,1.37)	0.778	1.86(1.45,2.38)	<0.001
Urea	1.00(0.98,1.01)	0.528	1.02(1.00,1.03)	0.066	1.04(1.02,1.06)	0.001	1.02(1.00,1.03)	0.105
D-dimer	1.00(1.00,1.01)	0.337	1.00(1.00,1.01)	0.004	1.00(1.00,1.01)	0.288	1.00(1.00,1.01)	0.001

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; TBIL, total bilirubin; CI, confidence interval.



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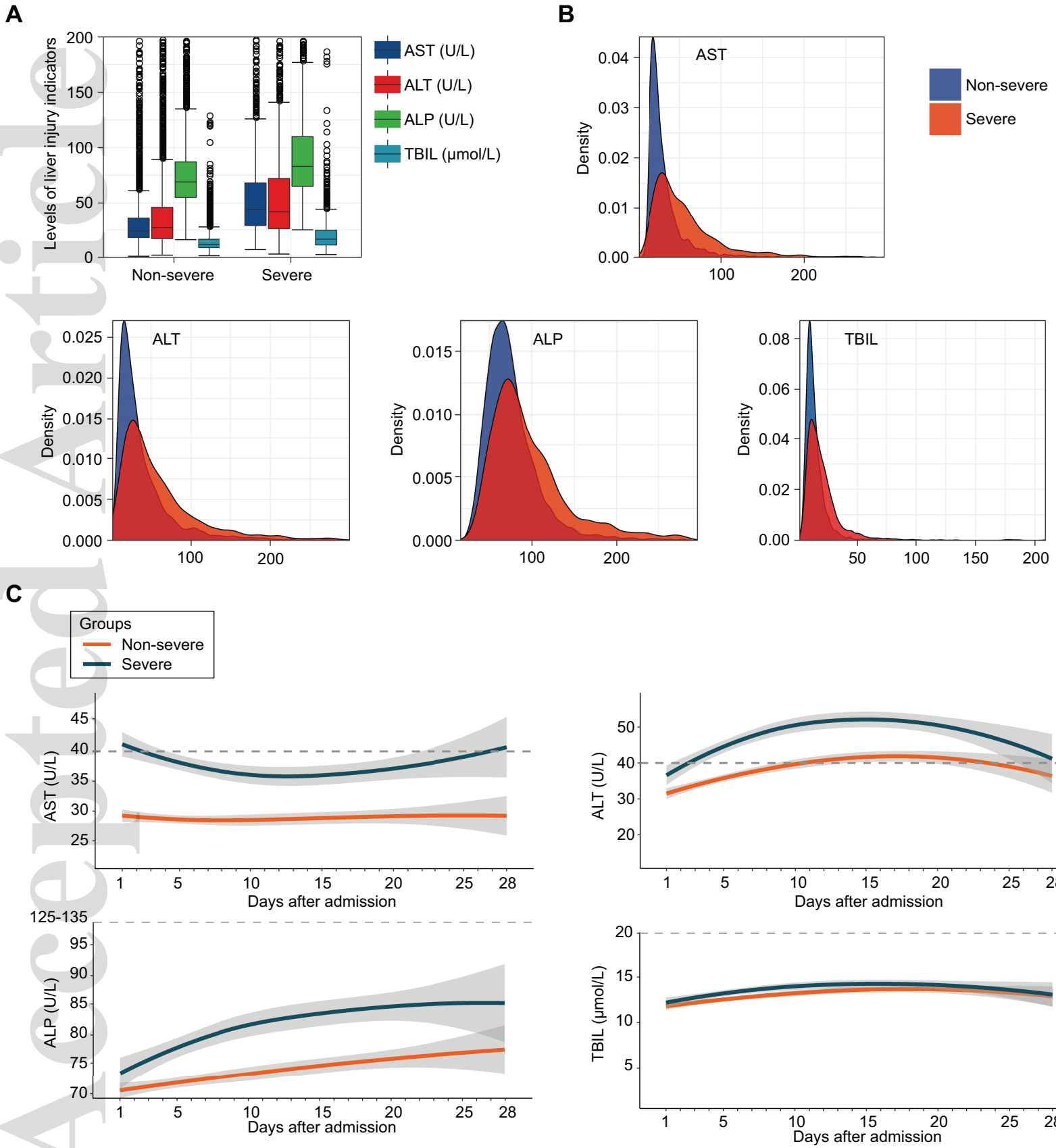

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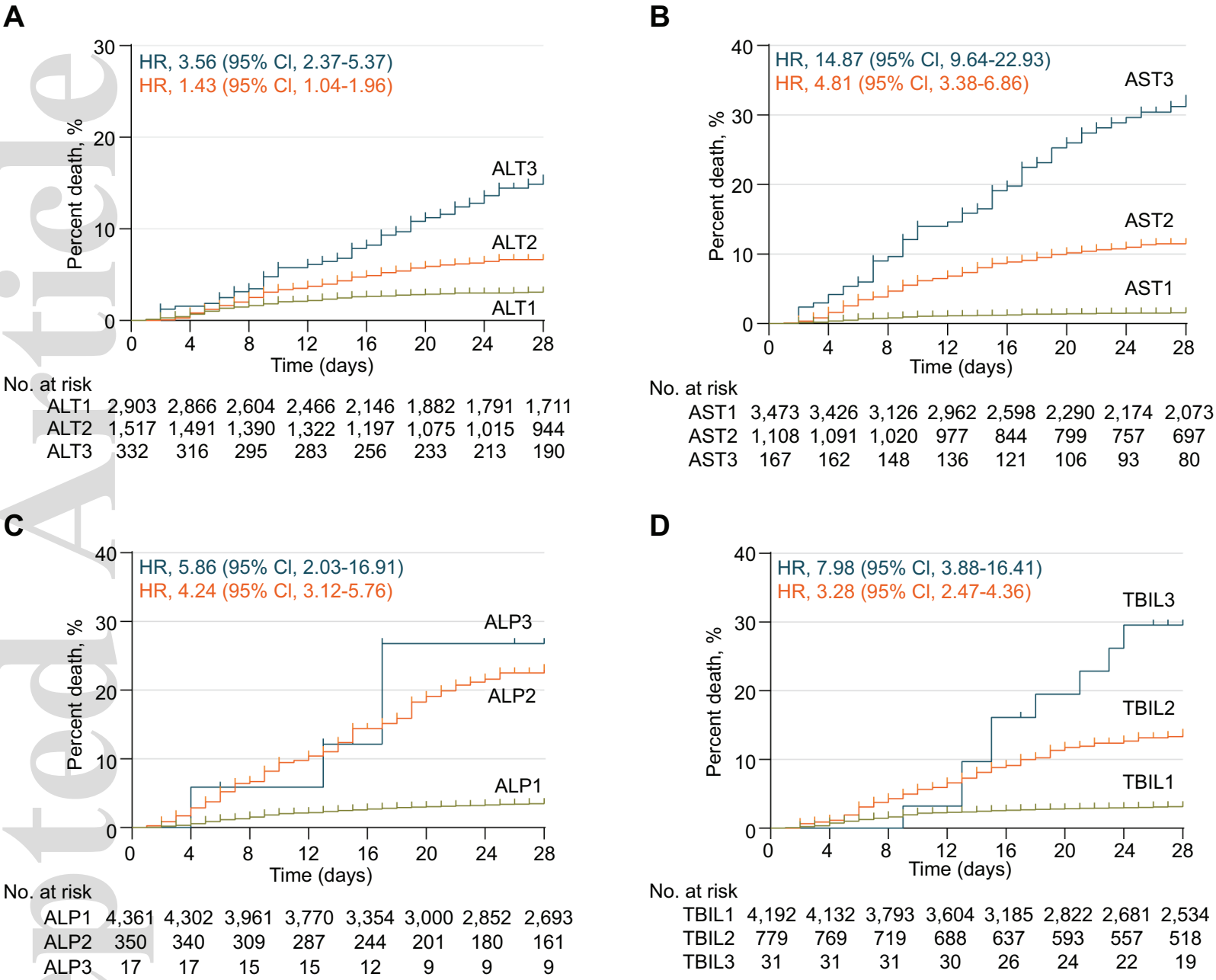

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